Polychlorinated Biphenyl- and Triphenyl-Induced Gastric Mucosal Hyperplasia in Primates

Abstract. *Polychlorinated biphenyl or triphenyl ingestion by subhuman primates for 3 months produced hyperplasia and dysplasia of the gastric mucosa. The concentration of the biphenyl within the experimental diet was less than an order of magnitude greater than that occurring in random food samples sold in the United States and less than levels which have occurred in food products as a result of industrial accidents. The increased cellularity, abnormal dysplastic growth pattern, and invasion of the adjacent tissue region indicate compromised gastric function and are suggestive of an eventual neoplastic transformation.*

Polychlorinated biphenyls (PCB's) have been widely used in industry for over 40 years as sealants, heat transfer agents, plasticizers, adhesives, and dielectric fluids in capacitors and transformers. Global environmental contamination (*1*) and their presence within the food chain have occurred through industrial accidents and improper disposal and misuses of the compounds (*2*, *3*). Polychlorinated biphenyls were reported in the United States in coho salmon in 1969 and then in milk fat (28 parts per million), poultry and eggs (4.2 ppm), fish (35 ppm), and cereals (less than 1 ppm) (*2*). The Food and Drug Administration is presently removing from the market known contaminated food samples which exceed 5 ppm. However, as a result of occult environmental and food exposure, significant levels of PCB's (over 1 ppm in adipose tissue) are present in over 30 percent of random samples taken from the general population of this country (*4*). Two separate, well-documented industrial accidents resulted in high concentrations of PCB's in rice oil (2000 to 3000 ppm), which was subsequently consumed by over 1000 people (*5*), and in fish meal (14 to 30 ppm) used for poultry feed (*2*). The effects of PCB's on humans include acneform skin eruptions, pigmentation of nails and skin, eye discharge, generalized swelling, weakness, vomiting, diarrhea, weight loss, and fetal toxicity (*5*). Additional effects observed in experimental animals fed the compounds include hepatic porphyria in chickens and rabbits (*6*), proliferation of hepatic smooth endoplasmic reticulum in rats (*7*), mice, and monkeys (*8*), increase in certain hepatic enzyme activities in rats (*7*) and kestrels (*9*), neuropathy in rats (*10*), lymphopenia and immunosuppression in rabbits and guinea pigs (*6*), and estrogenic activity in the rat uterus (*11*). In the study reported here dermatologic alterations including alopecia, edema, and acneform lesions and hepatic alterations including organ hypertrophy and proliferation of the endoplasmic reticulum were observed in the subhuman primate. In addition, a previously unreported lesion, hyperplasia and dysplasia of the gastric mucosa, occurred in all animals that were fed diets containing the chlorinated biphenyls and triphenyls (PCT's).

Fig. 1. (A) Normal pyloric glands of the gastric mucosa (*M*) are separated from the submucosa (*S*) by the muscularis mucosae (*m*). (B) Following polychlorinated biphenyl ingestion the hyperplastic mucosal glands penetrate the muscularis mucosae to form mucus-filled cysts of the submucosa. Cells lining cyst similar to area indicated by arrow (→) are magnified in Fig. 2. (×40; scale represents 500 μm).

Male rhesus monkeys ranging in age from 1½ to 2 years and having an average weight of 2.9 kg were used in this study. Six animals were fed a diet containing 300 parts of PCB (Aroclor 1248) per million and six were given 5000 parts of PCT (Aroclor 5460) per million in the diet, for 3 months. The remaining three animals served as controls. During the course of the experiment the animals were given access to 400 g of the experimental diet daily. The animals continued to eat throughout the experimental period, although there was a decrease in body weight of approximately 15 percent in both of the experimental groups. Within 1 month, all of the PCB-fed animals, and within 6 weeks, the PCT-fed animals, had hair loss from the head, neck, and back. A progressive, generalized, subcutaneous edema, particularly of the face, was manifested as swollen eyelids and lips. A purulent discharge exuded from the eyes, and isolated acneform lesions were present on skin areas devoid of hair. Liver hypertrophy (2.3 percent of the body weight in controls; 4.5 percent in the PCB group; 5.6 percent in the PCT group) was attributed mainly to a proliferation of the smooth endoplasmic reticulum observed electron microscopically. Edematous thickening of the stomach wall and marked hypertrophy of the pyloric and fundic gastric mucosa occurred.

The hypertrophic gastric mucosa was several times thicker than the control mucosa and was composed of greatly elongated hyperplastic glands containing mucus-secreting cells (Fig. 1). The cells containing basilar positioned nuclei, abundant slightly acidophilic cytoplasm, large vacuoles, and a microvillous border abutted on a basal lamina. Prevention of discharge of the secretion owing to the depth and apposition

of the glands predisposed to the development of large mucous cysts. Glands of the fundic area which normally contain a variety of secretory cell types consisted primarily of mucus-secreting cells.

Widespread penetration of the muscularis mucosae and invasion of the submucosa by the mucosal epithelium (Fig. 1) was observed in the stomach of each experimental animal. Large cystic areas filled with mucus and lined with elongated mucus-secreting epithelial cells predominated in the submucosa. Other cells assumed a glandular pattern. Serial sections of the submucosal cysts demonstrated stratified arrangements of proliferating epithelial cells which penetrated the basal lamina and invaded the surrounding connective tissue of the submucosa (Fig. 2). Epithelial origin of the stratified cells was determined by the presence of nucleoli and similarity of the nuclei in size and shape to the nuclei of the epithelial cells lining the cysts. Occasionally, irregular hyperchromic nuclei and pleomorphic cells with mitotic figures were present in the cells of the stratified areas. The presence of inflammatory cells in the submucosa in proximity to the glandular and cystic changes was common.

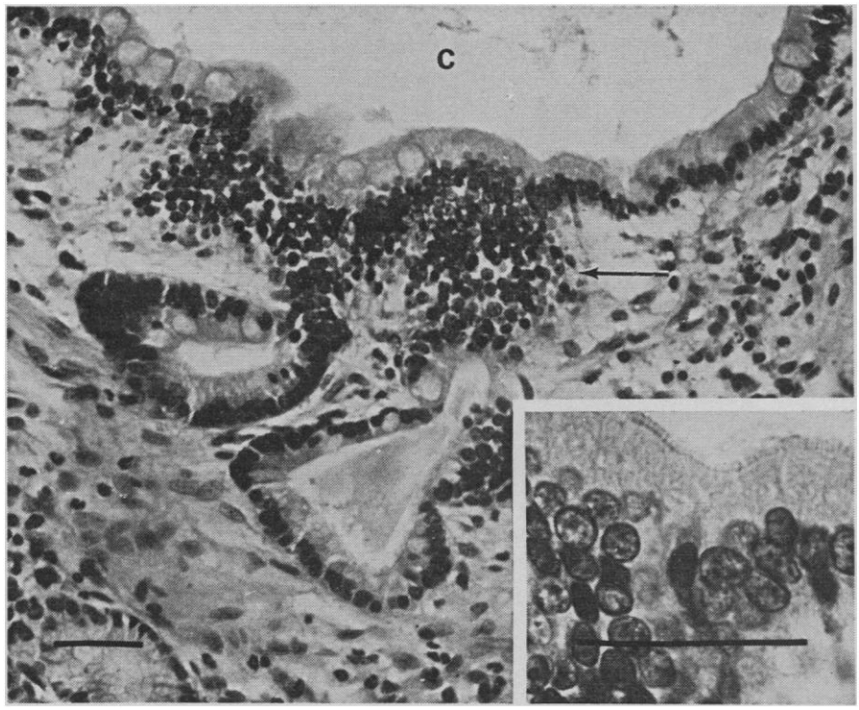

Fig. 2. Glandular epithelial cells that have extended from the mucosa into the submucosa encompass large cysts (*C*). In some areas (→) the epithelial cells are stratified and penetrate into the connective tissue of the submucosa. The cell nuclei of the stratified area is similar in size and appearance to that of the simple columnar epithelium that lines the remainder of the cyst (see inset). Serial sections of the tissue confirmed the stratified arrangement of the epithelial cells (×250, inset ×640; scale represents 50 μm).

The increased cellularity of the mucous glands with invasion of the muscularis mucosae and accompanying inflammation noted above is histologically described as a hypertrophic gastritis. The extension of the mucosal epithelial cells into the submucosa and the presence of irregular stratified arrangements of epithelial cells within the submucosa are distinctly dysplastic patterns. The experimental concentration of biphenyls (300 ppm) within the diet which was sufficient to produce these conditions in subhuman primates in 3 months is about ten times the levels that have occurred in samples of milk (28 ppm) and of fish (35 ppm) reported by the U.S. Food and Drug Administration (*2*). This concentration is much less than the levels that have occurred in food products due to industrial accidents (2000 to 3000 ppm) (*5*).

The magnitude of the chronic effects which could be produced by PCB-induced hypertrophic gastritis is as yet undetermined. The nausea and vomiting following human consumption of PCB's are possibly a result of the gastric irritations. Weight loss by the experimental monkeys and human patients exposed to the PCB's may be related to gastritis. Replacement of the parietal cells by the mucus-secreting cells which occurred in the fundic glands of the more severely affected animals may result in achlorhydria and eventual pernicious anemia owing to the lack of intrinsic factor necessary for vitamin B_{12} absorption. Invasion of the muscularis mucosae and submucosa by the epithelial elements may lead to loss of integrity of the gastric wall with eventual erosion, ulceration, and hemorrhage, as was the case in monkeys fed chlorinated biphenyl dioxins (*12*).

Because interest in these environmental contaminants is only recent, investigative efforts have not yet determined the long-term carcinogenic potential of PCB's and PCT's. The association of chronic irritation with cancer, particularly of the stomach, cervix, oral mucosa, and bronchial epithelium, is well documented. These dysplastic cellular abnormalities of the hypertrophic gastric mucosa are likely due to chronic irritation but are at present short of neoplastic transformation. The development of hypertrophy, hyperplasia, and dysplasia of the gastric mucosa of subhuman primates necessitates clarification of the carcinogenic potentials of these compounds.

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References and Notes

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